2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO FLUORINE, HYDROGEN FLUORIDE, AND FLUORIDES IN THE UNITED STATES

Fluorine is the most electronegative and reactive of all elements. It is a pale yellow gas that is used in rocket fuels and in making glass, enamel, and bricks. Fluoride is the ionic form of fluorine. Hydrogen fluoride is a colorless gas that readily dissolves in water to form hydrofluoric acid. Anhydrous hydrogen fluoride is used in the production of most fluorine-containing chemicals and in the production of refrigerants, herbicides, pharmaceuticals, high octane gasoline, aluminum, plastics, electrical components, and fluorescent light bulbs. Aqueous hydrofluoric acid is used in stainless steel pickling, glass etching, and metal coatings. Volcanoes are the major natural source of hydrogen fluoride. The major anthropogenic sources of hydrogen fluoride is the combustion of coal, aluminum production plants, and phosphate fertilizer plants. The general population is exposed to very low levels of hydrogen fluoride. Populations living near industrial sources of hydrogen fluoride, including coal burning facilities, as well as workers in fluoride processing industries, may be exposed to higher levels of hydrogen fluoride in the air. Additionally, vegetables and fruits grown near these sources may contain higher levels of fluoride, particularly from fluoride-containing dust settling on the plants.

Fluoride salts, generically referred to as fluorides, are naturally occurring components of rocks and soil. They enter the atmosphere through volcanic emissions, resuspension of soil by wind, and runoff from weathering of fluoride-containing rocks and soil. Sodium fluoride is a white solid that is readily soluble in water. One of the principal uses of sodium fluoride is the fluoridation of public water for the prevention of dental caries. The population is generally exposed to low levels (~1 ppm) of fluoride through consumption of drinking water, food, and dentifrices. Numerous studies support the effectiveness of water fluoridation in preventing coronal and root caries in children and adults. Individuals who consume a large quantity of tea may also be exposed to higher levels of fluoride since tea plants accumulate fluoride. Industrial uses include: flux for deoxidizing rimmed steel and in the manufacture of vitreous enamels, pickling of stainless steel, wood preservative compounds, casein glues, and coated papers. Sodium fluoride has been used as an insecticide, rodenticide, and fungicide. Populations living near industrial sources of fluoride may be exposed to airborne fluoride.

2.2 SUMMARY OF HEALTH EFFECTS

The following section lists health effects caused by exposure to fluorine, hydrogen fluoride, and fluoride. Readers should keep in mind that adverse health effects generally occur at high exposure levels.

Fluorine. Limited data exist on the toxicity of fluorine; the two possible routes of exposure to fluorine are inhalation or dermal contact with the gas. Fluorine gas is extremely irritating; human and animal data suggest that the primary health effects of acute fluorine inhalation are nasal and eye irritation (at low levels), and death due to pulmonary edema (at high levels). In animals, renal and hepatic damage have also been observed.

Hydrogen Fluoride. Hydrogen fluoride is highly corrosive and like fluorine, the primary effects are tissue damage resulting from direct contact. Acute inhalation exposure can result in bronchiolar ulceration, pulmonary hemorrhage and edema, and death. Gastrointestinal irritation has also been observed in humans exposed to low levels of hydrogen fluoride. Direct contact of hydrogen fluoride/hydrofluoric acid with the eyes or skin can produce skin burns, “burning sensation”, and lacrimation. In addition to these direct contact effects, exposure to hydrogen fluoride can result in skeletal and cardiac effects. Skeletal fluorosis has been observed in workers exposed to hydrogen fluoride and fluoride dusts. Exposure to very high levels of hydrogen fluoride/hydrofluoric acid can result in severe cardiovascular effects, which are attributed to a combination of hypocalcemia and hyperkalemia; cardiac arrhythmias have been seen in humans following hydrofluoric acid splashes in the face region; and myocardial necrosis and congestion were observed in rabbits. Hepatic (fatty degeneration and necrosis) and renal effects (tubular degeneration and necrosis) have also been observed in animal studies.

Although excess cancer rates have been reported in some occupational groups exposed to hydrogen fluoride and fluoride dusts, these studies were not controlled for the multiple substance exposures to which industrial workers are generally exposed. Because of these multiple exposures and the problems inherent in all occupational studies in identifying appropriate reference populations, only limited evidence from such studies is specifically relevant to the investigation of possible carcinogenic effects of long-term dermal exposure to hydrofluoric acid and inhalation exposure to hydrogen fluoride and/or fluoride dusts in human beings. The International Agency for Research on Cancer has determined that the carcinogenicity of fluoride to humans is not classifiable.

Fluoride. During the past 50 years, numerous studies have provided strong evidence that water fluoridation (at approximately 1 ppm) results in a notable reduction in coronal and root surface caries in children and adults. Furthermore, communities that no longer fluoridate their water have experienced an

increase in caries (DHHS 2000). However, at higher levels of exposure, fluoride might cause adverse health effects. The main health concern regarding fluoride is likely to be from excessive chronic oral exposure in drinking water. Acute oral exposure to very large doses of sodium fluoride as a result of accidental or intentional poisoning can produce gastrointestinal effects and death at high doses, but the dosage in such cases is often difficult to estimate. Excessive exposure to fluoride in children under 6 years old can result in mottling of their permanent teeth. The severity of mottling increases with fluoride dose and ranges from almost invisible opaque white spots to teeth with brown spots and pitting. Chronic exposure to fluoride in drinking water at doses above 2 ppm during development of the deciduous and permanent teeth, coupled with additional fluoride exposure from food and dental products, can result in visible mottling. Recent studies have found small white spots in about 20% of the children exposed to water containing 1 ppm fluoride; <1% may have brown spots. Mild dental fluorosis is considered a cosmetic effect; it is not necessarily a precursor to skeletal fluorosis, but may be a clinical indicator of exposure of children to excess fluoride.

Due to the deposition of significant amounts of fluoride in bone, the primary target system for intermediate and chronic exposures of both humans and several animal species is the skeletal system. Some recent studies suggest that elderly women and men in communities with fluoridated water may have an elevated risk of hip fractures, but other studies have not found this effect. Long-term, high level exposure can lead to skeletal fluorosis.

Additional systemic effects that have been observed in humans and/or animals include symptoms of gastrointestinal irritation (nausea, vomiting, gastric pain), severe cardiac effects (e.g., tetany, decreased myocardial contractility, cardiovascular collapse, ventricular fibrillation) at or near lethal doses, and parenchymal degeneration in the liver. Reproductive effects have been observed in humans and animals. An ecological study found a significant association between fluoride levels in municipal drinking water and decreases in fertility rates. In animal studies, alterations in reproductive hormone levels, histology of the testes, spermatogenesis, and male fertility have been observed. In addition, while studies in laboratory animals (rats and rabbits) have not found developmental effects, developmental effects have been seen in wild and domestic animals (cattle and mink).

Numerous ecological studies have examined the possible association between fluoridated water and cancer. The weight of the evidence indicates that fluoridation of water does not increase the risk of developing cancer. These studies were not designed to detect small increases in cancer occurrences; the most sensitive studies required increases of 10–20%. A 2-year study in rats found a weak, equivocal fluoride-related increase in the occurrence of osteosarcomas in male rats, and no evidence of carcinogenicity in female rats or male or female mice.

In response to public health concerns raised by equivocal findings of carcinogenicity in male rats, the U.S. Department of Health and Human Services assembled a committee of scientists to evaluate the risks and benefits of oral exposure to fluoride (DHHS 1991). The report concluded that:

> "Extensive studies over the past 50 years have established that individuals whose drinking water is fluoridated show a reduction in dental caries. Although the comparative degree of measurable benefit has been reduced recently as other fluoride sources have become available in nonfluoridated areas, the benefits of water fluoridation are still clearly evident. The health and economic benefits of water fluoridation accrue to individuals of all ages and socioeconomic groups, especially to poor children."

The policy recommendations offered by the report include:

> "The U.S. Public Health Service should continue to recommend the use of fluoride to prevent dental caries."
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> "The U.S. Public Health Service should continue to support optimal fluoridation of drinking water. Currently, the optimal level for water fluoridation is between 0.7–1.2 parts per million, depending on mean daily air temperature for a geographic area."
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> "The U.S. Public Health Service should sponsor a scientific conference to recommend both the optimal level of total fluoride from all sources combined (including drinking water) and the appropriate usage of fluoride containing dental products in order to achieve the benefits of reduced dental caries and to minimize the occurrence of dental fluorosis."
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> "In accordance with prudent health practice of using no more than the amount necessary to achieve a desired effect, health professionals and the public should avoid excessive and inappropriate fluoride exposure."
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> "The U.S. Food and Drug Administration should review the labeling required for toothpaste and other fluoride containing products to ensure that the public has adequate knowledge to make informed decisions about their use, especially for young children (those under six years of age)."
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> "Communities with high natural fluoride levels in the public drinking water supply should comply with EPA regulations as mandated by the Safe Drinking Water Act. The current primary and secondary maximum contaminant levels are 4 and 2 parts per million, respectively."

The 2000 Surgeon General's Report (DHHS 2000) on Oral Health reaffirms the benefits of fluoride, when used at recommended levels, in reducing dental caries in the United States. The Surgeon General's Report concludes:

> "Given the modest cost of less than 1 dollar per person per year to fluoridate water systems serving most people, community water fluoridation is recommended as a very effective and cost-effective method of preventing coronal and root caries in children and adults."

Respiratory, Gastrointestinal, Dermal, and Ocular Effects. Fluorine, hydrogen fluoride, and hydrofluoric acid are extremely irritating chemicals and can cause tissue damage after direct contact. Inhalation exposure to fluorine has been observed to cause respiratory tract irritation in people, and dyspnea and lung congestion in animals. Pulmonary and nasal irritation have also been reported following repeated exposures for about 30 days. However, human and animal data suggest that preexposure to lower levels can reduce the respiratory effects.

Acute lethal inhalation exposure of humans to hydrofluoric acid has produced pulmonary edema. Acute inhalation exposure to hydrofluoric acid has produced nasal irritation, respiratory distress, pulmonary congestion, and intraalveolar edema in rats, rabbits, and guinea pigs. Similarly, intermediate-duration inhalation exposure caused pulmonary hemorrhage and signs of inflammation. The respiratory effects of hydrofluoric acid are attributed to its highly corrosive properties. Chronic exposure to hydrogen fluoride and cryolite dust has resulted in impaired lung function in workers.

Gastrointestinal effects have been observed following inhalation and oral exposure to fluorides. Populations living near a smelter emitting hydrogen fluoride or exposed during an accidental release of hydrogen fluoride have reported gastrointestinal effects, including nausea, gastrointestinal distress, and vomiting. Although no studies examined the gastrointestinal tract following oral exposure to hydrofluoric acid, it is likely that ingestion would result in severe gastrointestinal effects due to its caustic properties.

Gastrointestinal effects have also been observed following both acute and chronic oral exposure to excessive fluoride; the most commonly reported effects are nausea, vomiting, and gastric pain. The irritation of the gastric mucosa is attributed to fluoride (as sodium fluoride) forming hydrofluoric acid in the acidic environment of the stomach. Vomiting, nausea, and diarrhea are the most commonly reported gastrointestinal effects of individuals ingesting <1 mg/kg fluoride. Endoscopic examination of individuals consuming high levels of sodium fluoride revealed minute hemorrhages and erosions in the stomach. Marked stomach irritation (ulcers, necrosis) has been observed in rats exposed to fairly high levels of sodium fluoride, but not after chronic exposure to lower doses, suggesting that the concentration of sodium fluoride in the stomach may strongly influence its gastrointestinal toxicity.

Dermal and ocular effects have occurred in humans exposed to hydrofluoric acid dermally and to atmospheric fluorine or hydrogen fluoride. Because hydrofluoric acid is caustic and the fluoride ion is rapidly absorbed through the skin, severe burns, tissue damage, and even death can result. The severity of the damage depends on a number of factors (e.g., length of exposure, strength of the acid solution, percentage of the body exposed, and treatment utilized). Animal data support the human data and indicate that hydrofluoric acid produces severe skin and ocular damage, which, if severe enough, is not reversible.

Skeletal Effects. Human and animal data clearly indicate that fluoride accumulates in the teeth and skeleton. Numerous studies have shown that the increase in fluoride levels in teeth results in a decreased occurrence of dental caries and the topical effect of frequent exposure to low-dose fluoride that protects the teeth from demineralization and helps to remineralize already damaged enamel. Levels of up to about 1 ppm in drinking water have been associated with a decreased number of dental cavities. Drinking water fluoride levels that reduce the incidence of dental caries can sometimes result in dental fluorosis. At higher fluoride concentrations, changes in tooth color and surface irregularities are visible. Dental fluorosis only occurs in children during the development of their deciduous and/or permanent teeth. Mild dental fluorosis is considered a cosmetic effect not causing functional damage to the teeth. Fluoride causes dental fluorosis by impairing the work of ameloblast cells. High fluoride levels can increase the susceptibility to dental caries resulting from an increase in porosity and hypoplasia of the teeth. Dental fluorosis has also been observed in animal studies.

In bone, fluoride replaces the hydroxyl ion in hydroxyapatite to form fluorapatite, thus changing the physicochemical properties of the bone. Ingestion (and inhalation) of large doses of fluoride for an extended period of time can result in thickened bones and exostoses (skeletal fluorosis). Signs of skeletal fluorosis range from increased bone density to severe deformity, known as crippling skeletal fluorosis. Crippling fluorosis is characterized by complete rigidity of the spine. Reported cases are found almost exclusively in developing countries, particularly India, and are often associated with malnutrition. It is generally stated that a dose of 20–80 mg/day (equivalent to 10–40 ppm in the water, for a person who ingests 2 L/day) is necessary for the development of crippling skeletal fluorosis, but individual variation, variation in nutritional status, and the difficulty of determining water fluoride levels in such situations make it difficult to determine the critical dose.

A large number of epidemiology studies have attempted to examine the relationship between fluoride in drinking water and the risk of bone fracture. The results of these predominantly ecological studies are inconsistent. Studies have found increases and decreases in hip fracture rates among older women living in areas with fluoride in the drinking water, as compared to women living in areas with very low levels of fluoride in the drinking water (<0.3 ppm). Other studies have not found an effect of fluoride on fracture risk. A relationship between fluoride in drinking water and bone fractures cannot be established from these studies. A number of other studies have examined the efficacy of using fluoride to treat osteoporosis because fluoride exposure results in increased bone density. In studies using high levels of fluoride (34 mg/day), an increased risk of nonvertebral fractures has been found. The risk of vertebral fractures was not affected. These studies also found increases in lumbar spinal and femoral head and trochanter bone mineral density and decreases in radium bone mineral density. Animal studies have shown that the increase in bone density was negatively associated with bone strength, suggesting that the new bone was of inferior quality.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Fluorine

- An acute-duration inhalation MRL of 0.01 ppm fluorine was derived for fluorine.

Irritation appears to be the primary effect following acute inhalation exposure to fluorine. The observed effects include eye, skin, and nasal irritation in humans intermittently exposed to $50 ppm for 0.5–3 minutes and dyspnea and lung congestion in rats and mice exposed to 47–175 ppm fluorine for 5–60 minutes. The threshold for the respiratory effects appears to be duration-related. Necrosis was also observed in the liver parenchymal tissue and in the renal tubules of rodents acutely exposed to fluorine. In general, the liver and kidney effects occurred at higher concentrations than the respiratory effects.

The Keplinger and Suissa human study was selected as the basis of an acute-duration inhalation MRL for fluorine. This study reported slight eye and skin irritation (considered a dermal effect) in five volunteers exposed to 23 ppm for 3–5-minute periods every 15 minutes for 2–3 hours; nasal irritation was reported at concentrations of 67 ppm fluorine (3-minute exposure) and higher. The severity of the irritation was concentration-related, and irritation was not reported at 10 ppm for 3, 5, or 15 minutes. The NOAEL of 10 ppm for the 15-minute exposure and an uncertainty factor of 10 to account for intrahuman variability were used to derive an acute-duration inhalation MRL of 0.01 ppm fluorine.

Longer-duration exposure studies are limited to lethality studies and an occupational exposure study in which the workers and the controls were exposed to uranium hexafluoride and hydrogen fluoride. These data are inadequate for the derivation of intermediate-duration and chronic-duration inhalation MRLs for fluorine.

Hydrogen Fluoride.

- An acute-duration inhalation MRL of 0.03 ppm fluoride was derived for hydrogen fluoride.

The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. There are limited data on the acute toxicity of hydrogen fluoride in humans. One human subject reported nasal irritation following exposure to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days. Several animal studies report respiratory effects in rats. Mild nasal irritation was reported in rats exposed to 120 ppm fluoride as hydrogen fluoride for 60 minutes; the LOAELs for nasal irritation were higher for shorter

durations. Respiratory distress was observed in rats exposed to 50% of the LC_{50} value for 5, 15, 30, or 60 minutes (2,310, 1,339, 1,308, and 465 ppm fluoride, respectively). Midtracheal necrosis was reported in rats exposed to 902 or 1,509 ppm fluoride as hydrogen fluoride for 2 or 10 minutes using a mouth breathing model with a tracheal cannula. These effects were not observed when the tracheal cannula was not used. A 60-minute exposure study was selected as the basis of an acute-duration inhalation MRL for hydrogen fluoride. In this study, general discomfort, pawing at the nose and tearing from the eyes were observed during exposure to 120 ppm fluoride as hydrogen fluoride. At 98 ppm, the study authors noted that there was occasional pawing at the nose; this concentration was considered a NOAEL. A $NOAEL_{HEC}$ was calculated by multiplying the NOAEL by the RDGR and adjusting for less than 24-hour exposure. The $NOAEL_{HEC}$ was divided by an uncertainty factor of 30 (3 for interspecies extrapolation using dosimetric adjustments and 10 for intrahuman variability) to yield an acute-duration inhalation MRL of 0.03 ppm fluoride as hydrogen fluoride.

- An intermediate-duration inhalation MRL of 0.02 ppm fluoride was derived for hydrogen fluoride.

There are limited data on the long term toxicity of hydrogen fluoride. Slight nasal irritation was reported by volunteers exposed to an average concentration of 2.98 ppm fluoride, 6 hours/day for 15–50 days. In rats, rabbits, and dogs, pulmonary hemorrhages were observed after exposure to 31 ppm fluoride for 6 hours/day, 6 days/week for 5 weeks. In the study selected as the basis of an intermediate-duration inhalation MRL for hydrogen fluoride, five volunteers were exposed to average hydrogen fluoride concentrations of 0.85–7.7 ppm fluoride; the mean of the average concentrations was 2.98 ppm fluoride. A duration-adjusted LOAEL of 0.75 ppm fluoride was calculated by adjusting the mean concentration for intermittent exposure (an assumption was made that the subjects were exposed daily to hydrogen fluoride). This duration-adjusted LOAEL was divided by an uncertainty factor of 30 (3 to account for the use of a LOAEL for slight irritation and 10 for intrahuman variability) to derive an MRL of 0.02 ppm fluoride for hydrogen fluoride.

No chronic-duration studies were located for hydrogen fluoride; thus, a chronic-duration inhalation MRL was not derived.

Fluoride

- No inhalation MRLs were derived for fluoride.

Several occupational exposure studies examined fluoride toxicity in aluminum potroom workers. Interpretation of these studies is limited by co-exposure to hydrogen fluoride and other chemicals

including aluminum. No animal studies examined the toxicity of inhaled fluorides. Thus, inhalation MRLs were not derived for this chemical.

Oral MRLs

Hydrogen Fluoride/Hydrofluoric Acid

- No oral MRLs were derived for hydrogen fluoride/hydrofluoric acid

Only lethality studies were identified for hydrogen fluoride/hydrofluoric acid, precluding derivation of oral MRLs for this chemical.

Fluoride

- A chronic-duration oral MRL of 0.06 mg fluoride/kg/day was derived for fluoride.

There are limited data on the acute toxicity of fluoride in humans and animals. The only nonlethal adverse effect that was identified was a decrease in modulus of elasticity in the bones of weanling rats exposed to 9.5 mg fluoride/kg/day as sodium fluoride in drinking water for 2 weeks. The remaining nonlethality studies examined reproductive and developmental end points and did not find report adverse effects. Because the available studies examined a limited number of end points (skeletal, reproductive, developmental), identification of the critical effect cannot be made with confidence. Additionally, the Guggenheim et al. study only tested one dose level; thus, a dose-response relationship can not be established for the observed skeletal effects.

Several studies have examined the toxicity of sodium fluoride following intermediate-duration exposure in laboratory animals. These studies have identified a number of potentially sensitive targets of fluoride toxicity. The lowest identified LOAELs are 0.5 mg fluoride/kg/day for thyroid effects in rats exposed to sodium fluoride in drinking water for 2 months and 0.80 mg fluoride/kg/day for increased bone formation in mice exposed to sodium fluoride in drinking water for 4 weeks. Neither study identified a NOAEL. Derivation of an intermediate-duration MRL from either study would result in an MRL that is lower than chronic-duration oral MRL.

A number of human studies have investigated the toxicity, particularly potential skeletal toxicity, of fluoride. The vast majority of these studies were ecological studies examining the possible relationship between fluoride in drinking water and the occurrence of hip fractures. These studies, as well as retrospective cohort studies, have found decreases, increases, and no effect on hip fracture occurrence in

communities consuming fluoridated water. Limitations in the study designs of many of these studies preclude using these data to establish a causal relationship between fluoride and risk of hip fractures. In addition to these epidemiology studies, several human experimental studies have examined the effect of fluoride administration for the treatment of osteoporosis. One study found significant increases in lumbar spine and femoral head and trochanter bone mineral density, decreases in radius bone mineral density, no effect on vertebral fracture rate, and increases in nonvertebral fracture rate among postmenopausal women with osteoporosis ingesting a capsule containing 34 mg fluoride/day as sodium fluoride for 4–6 years. Another study did not find any effect on bone mineral density or vertebral or nonvertebral fracture rates among postmenopausal women with spinal osteoporosis ingesting 34 mg fluoride/day as sodium fluoride. A meta-analysis of these data, as well as other clinical studies, found a significant correlation between exposure to high levels of fluoride and an increased relative risk of nonvertebral fractures. The LOAEL of 34 mg fluoride/day (0.56 mg fluoride/kg/day) was selected as the basis of a chronic-duration oral MRL for fluoride. The MRL of 0.06 mg fluoride/kg/day was derived by dividing the LOAEL by an uncertainty factor of 10 to account for the use of a LOAEL in a sensitive subpopulation.